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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	

ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/657,550	CHAUDRY, IMTIAZ	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,10-13,22-25,27-30,35 and 71-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-6, 10-13, 22-25, 27-30, 35, and 71-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/9/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 71-76 are pending. Applicant previously cancelled claims 2-3, 7-9, 16-21, 26, and 31-34, and 36-70. Applicant has newly cancelled claims 14-15. Applicant has amended claims 1, 10, 35, and 75. Receipt and consideration of Applicant's new IDS (submitted 10/9/09), amended claim set, and remarks/arguments submitted on August 13, 2009 are acknowledged. All rejections/objections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments.

Moot Rejections/objections

All rejections and/or objections of claims 14-15 cited in the previous office action mailed on April 13, 2009 **are moot**, because said claims have been cancelled.

Election/Restrictions

The election/restriction of record remains proper and is maintained at this time.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4-6, 10-13, 22-25, 27-30, and 35 **remain rejected** under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Armstrong, L. L.; Goldman, M. P.; Lance, L. L., Lexi-Comp, Inc.: Cleveland, 1999, pp 445-446) in view of Bernini et al. (U.S. Patent No. 6,464,958), Harris (WO 99/18971) (New IDS reference) and Osbakken et al. (US 2002/0061281).

Applicant Claims

Applicant claims an aqueous formulation comprising (a) 0.04% to 0.06% w/w of a suspended steroidal anti-inflammatory that is fluticasone or a pharmaceutically acceptable salt,

ester, enol, ether, enol ether, enol ester, acid, or base thereof characterized by the particle size distribution described in claim 1, (b) about 0.05 to about 150 mg of an antifungal agent(e.g. amphotericin beta), further comprising (c) a preservative, such as benzalkonium chloride (e.g. claims 23-24 and 28), (d) other excipients (e.g. dextrose, carboxymethylcellulose sodium, etc.), and (e) an antibiotic (claims 29-30), wherein the formulation is suitable for administration to the para-nasal mucosa.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of FLONASE®, the PDR®, the DIH, ad Osbakken are restated herein below.

FLONASE® is a commercially available nasal spray sold in a metering, atomizing, spray pump containing therein an aqueous suspension of suspended microfine fluticasone propionate (16 g bottle delivering 120 individual 50 microgram doses per actuation; i.e. **0.0375% w/w fluticasone propionate**), **microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, 0.25% w/w phenylethyl alcohol, wherein the aqueous suspension has a pH between 5 and 7** (PDR printout, pg. 1, "Description section"). The recommended dosage of FLONASE® for adults is 50 micrograms per nostril for a total **daily dosage of 200 micrograms**. Alternatively, the administration of two 100 microgram doses twice daily is also effective. Adolescents and children 4 years of age and older should begin with **100 microgram dosages** (1 spray per nostril per day), but may use 200 micrograms (2 sprays per nostril per day) if not adequately responding (PDR, pg. 7, "Dosage and Administration" section).

The DIH demonstrates that FLONASE® was a commercially available product at least as early as 1999. The DIH also sets forth that **neomycin sulfate** (pg. 721-722) was a known antibiotic at the time of Applicant's invention and that **acyclovir** (pgs. 26-28), **ganiciclovir** (pgs. 463-464), **foscarnet** (pgs. 454-456), **cidofovir** (pgs. 225-226), and **formivirsen** (pgs. 453-454) were all known antiviral agents at the time of Applicant's invention.

Bernini teaches a process for the preparation of suspensions of drug particles for **inhalation delivery**, providing **optimized particle size and distribution**. A further aspect of the invention is directed to a process for preparing micronized **sterile steroidal formulations** by gamma-irradiation (abstract; col. 1, lines 17-27; col. 4, lines 14-25).

Bernini teaches that a number of **inhalation formulations** have been marketed for some years for the administration of **steroidal anti-inflammatory agents** for the topical **treatment of rhinitis and/or sinusitis**. An example of these steroidal anti-inflammatory drugs includes **beclomethasone dipropionate** (BDP). These formulations can be administered in the form of a finely divided (i.e. micronized powder) **suspension in an aqueous phase** containing necessary surfactants (i.e. emulsifiers) and/or cosolvents. When intended for administration in the form of **metered dose aerosol sprays**, these sprays should also contain **a low-boiling propellant** (col. 1, lines 8-12, 17-20, and 22-26).

Bernini teaches that in the process of preparing her formulations an **aqueous solution**, which constituted the carrier optionally, contains **wetting agents, surfactants** (i.e. emulsifiers), **preservatives, stabilizing agents, buffers**, and can optionally be **sterilized**.

Bernini teaches that the degree of solid particle size reduction and the resulting particle size distribution of the formulations produced by her process can be optimized by controlling

several variables: (i) the type and size of the interaction chamber; (ii) the operating pressure; and (iii) the processing time and the number of cycles the material passed through. The process effects are also dependent on the physicochemical properties of the ingredients subjected to treatment, however pressure and process times can be modified to achieve the desired results (col. 2, lines 33-43).

Bernini teaches that it would be highly advantageous to provide aqueous suspensions of steroids to be delivered in single unit-dose preparations, because **sterility** is a requirement in greater demand for pharmaceutical formulations intended for **nebulization** (col. 4, lines 31-36).

Bernini teaches that BDP micronized formulations when subjected to gamma radiation at 2 to 9 KGy remain chemically stable (col. 5, lines 53-55). Bernini states that the invented method allows for the preparation of sterile micronized BDP suspensions (col. 6, lines 19-21). Other drugs, which can be used in Bernini's formulations and methods, include corticoid steroids, such as **fluticasone propionate**, and other inhalable anti-inflammatory steroids (col. 1, lines 17-27; col. 4, lines 14-25; claims 1, 2, and 5-6).

Bernini teaches that the BDP starting material used in her process has a particle size of less than 10 microns, **preferably less than 5 microns**. The formulations for inhalation resulting from her invented process can be used to treat any **allergic** and/or inflammatory **condition of the nose** or the lungs (col. 6, lines 33-43).

Osbakken teaches **pharmaceutical compositions** are described that comprise one or more active ingredients including an **anti-infective agent, anti-inflammatory agent, and antibiotic combinations** or combinations of others of these classes of ingredients, especially

compositions **formulated as a solution or suspension** in a unit dose for aerosol administration to treat chronic sinusitis (abstract).

Osbakken teaches that sinusitis is an inflammation of the membrane lining one or more **paranasal sinuses (i.e. paranasal mucosa)**, and there are three principle kinds of sinusitis: acute, recurrent acute, and chronic [0004]. Therefore, it is obvious that the term rhinosinusitis encompasses sinusitis as in a genus-species relationship, wherein sinusitis is a species of the genus rhinosinusitis. Species are obvious over the genius.

Osbakken teaches that bacteria commonly associated with acute sinusitis, and that, although less common fungal sinusitis does occur and is often associated with infections caused *by Aspergillus, Vurvularia, Bipolaris, Exserohilum, Metarrhizium anisopliae,* and *Mucormycosis* fungi [0007]-[0008]. The primary objectives for the treatment of sinusitis are reduction of swelling, eradication of infection, draining of the sinuses, and ensuring that the sinuses remain open [0015]. Nebulization therapy is a conventional treatment for pulmonary infections and is also known to have been **used for sinus infections**, with few systemic side effects [0026].

Osbakken teaches that it had been suggested previously in the prior art to use small **aerosol particles of about 2-4 microns** in the treatment of sinusitis. See paragraphs [0027]-[0029], especially [0029].

Osbakken teaches that the use of synergistic antibiotic combination is desirable; because it allows for the treatment of more difficult infections (e.g. infections due to multiple-antibiotic-resistant organisms) and lower dosages, thereby reducing the probability of toxicity complications, treatment time, and therapy cost. For example, **cefuroxime and gentamicin**,

either individually or in combination with other agents, have been used to treat patients with sinusitis [0066]-[0068].

Osbakken teaches that his invention involves the **topical delivery of medications to the nasal cavity and sinuses** by aerosolizing **aqueous solutions or suspensions** of the medications taught. The aerosolized anti-infective particles are surprisingly effective when they have a mass median aerodynamic diameter (MMAD) of about 1.0 to 5.0 microns [0081]. Aerosolization/atomization of the formulations for nasal inhalation by a patient will result in liquid aerosol cloud particles having a MMAD of preferably between **about 0.5 microns and 10 microns**. Examples of suitable medicaments include **amphotericin beta (anti-fungal), cefuroxime (antibiotic), ciprofloxacin (antibiotic), tobramycin (antibiotic), cefoperazone (antibiotic), erythromycin (antibiotic), gentamycin (antibiotic)** [0085], **fluticasone (anti-inflammatory), and beclomethasone (anti-inflammatory)** [0139]. An exemplary formulation is described in [0178] and comprises **amphotericin beta (10 mg unit dose)**, hydrocortisone sodium succinate (50 mg dose in 3 ml sterile water) together with an anti-inflammatory agent. **Preferable dosage ranges** of various active agents including **amphotericin beta, beclomethasone, fluticasone, fluconazole, itraconazole, aztreonam, cefepime, doxycycline, tobramycin, vancomycin**, etc. are taught in Table-1.

Osbakken teaches that if necessary, osmotic pressure may then be raised to fall within a preferred range **by adding NaCl, dextrose, or other salts** to the liquid [0096]. Surfactants can be used as dispersing agents, solubilizing agents, and spreading agents. Some examples of surfactants are: PEG 400, sodium lauryl sulfate, spans (20-40-60 etc), tweens (**polysorbates, 20-**

40-60 etc), tyloxapol, propylene glycol, and **benzalkonium chloride**. Benzalkonium chloride is also a preservative.

Osbakken teaches in [0104] a general preparation of his invented formulations, wherein after determining the medications to be used in the formulation, each ingredient is weighed/measured individually, added together, mixed with diluent (e.g. **sterile water**), filtered with a coarse filter, and then a fine filter (5 micron, 2 micron, 1 micron, 0.45 micron, or 0.22 micron). The preparation is tested to ensure it is within the established parameters for surface tension, osmolarity, pH, and sodium chloride equivalency. To prepare a unit dose, the ingredients of such formulations generally will be dissolved in a solvent such as water or saline solution, in a volume between about 0.5 and 6.0 ml.

Osbakken teaches a **method of treating a mammal suspected or diagnosed as having chronic sinusitis** comprising the step of **administering** to the patient the pharmaceutical composition of any one of claims 1 or 2, by aerosolization using a nebulizer, which delivers aerosol particles of between about 1 to 5 microns in average diameter in claim 16 of US-2002. Osbakken also teaches in [0235] that **the medication is nebulized three times daily** and that the therapeutic treatment was continued for a total of seven days.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

The product information concerning FLONASE® is silent as to the particle size distribution of suspended beclomethasone. The product size distribution is either inherent to FLONASE® or it is rendered obvious by the teachings of Bernini as further articulated below. FLONASE® lacks the teaching of further comprising an antifungal agent or an antibiotic. This

deficiency is cured by the teachings of Osbakken, which has been provided as a supporting document to show what was known in the art regarding the treatment of rhinitis/sinusitis. Harris is provided as a supporting reference to demonstrate particle sizes recognized in the art as being suitable for nasal administration.

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to modify the compositions of FLONASE®/Bernini with the teachings of Osbakken, because it was well-known at the time of the instant invention that sinusitis is a species of rhinosinusitis (i.e. rhinitis) and is characterized by inflammation of one or more membranes of the paranasal sinuses (i.e. paranasal mucosae) that can be caused by microbial infection (i.e. fungal or bacterial infection). Using what was readily known to the ordinary skilled artisan at the time of the instant invention, an ordinary skilled artisan would have recognized that the underlying cause of sinusitis or rhinitis could be treated by the inclusion of an anti-microbial agent, such as an anti-fungal agent (e.g. amphotericin beta) or an antibacterial (e.g. doxycycline) in a therapeutically effective dosage. Thus, despite the fact that Osbakken focuses its teachings on aqueous solutions that are filtered, an ordinary skilled artisan would nonetheless have been motivated to modify FLONASE® to incorporate a therapeutically effective amount of an anti-fungal agent and/or an antibacterial to obtain a composition suitable for treating not only the inflammation resulting from an infection, but also suitable for treating the underlying cause of the inflammation (i.e. a fungal and/or bacterial infection). An ordinary skilled artisan would have had a reasonable expectation of success upon modification of the

FLONASE®/Bernini composition to further comprise an anti-fungal or antibacterial agent because these are art-recognized therapeutics for treating fungal and bacterial infections and are known in combination with anti-inflammatory steroids.

Regarding Applicants' data it is clear that the performance of both high and low-dose FLONASE® vis-à-vis the high and low dose formulations of Applicants' invention result in clinically comparable and in some cases indistinguishable results (see for example data points in Applicants' figure 1 at days 7, 10, and 12-14). Applicant has asserted that the claimed particle size distribution results are unexpected. The difference between the low dose and high dose data is that the high dose data is associated with two dosing events of either FLONASE® or Applicant's formulation. It is noted that Applicant's data is limited to formulations comprising 0.050% w/w fluticasone (see Table 3 on page 30 of the specification of copending 10/414,682 incorporated by reference into the instant application).

Applicants' "quantified" subjective data is graphically presented in Figures 1-4 of copending application 10/414,682 has been considered by the Examiner. It is the Examiner's position that the data presented does not demonstrate unexpected results when compared to the prior art data (FLONASE®). The Applicants' data compared to FLONASE® exhibit the same pattern of fluctuations over a period of 2-14 days; is of a similar magnitude, and in several instances is the same (see, for example, data points at days 4, 5, 9, and 10). It is also noted that the data points are not displayed with error bars. The display of the uncertainty in the data points is deemed necessary because the data reported in Figures 1-4 are based upon a least squares mean analysis of the raw Total Nasal Symptom Scores (TNSS) (i.e. these are aggregate data), which are subjective data assigned values by patients on an arbitrary scale of 0 to 3, where 0

means no symptoms and 3 means "severe symptoms present," wherein these subjective data were manipulated using the ANOVA model. For this reason, wherein Applicants' subjective data for the invented compositions and the prior art data points are very similar in magnitude, it would be reasonable for one to conclude that these data points are the same within a margin of error. Furthermore, the general differences depicted in the Figures are merely a difference of degree at best and not a difference of kind. A difference of degree is not sufficient to support patentability. The difference between the low dose and high dose data is that the high dose data is associated with two dosing events of either FLONASE® or Applicant's formulation. It is noted that Applicant's data is limited to formulations comprising 0.050% w/w fluticasone (see Table 3 on page 30 of the specification of copending 10/414,682 incorporated by reference into the instant application). Contrary to Applicant's statements, Applicant's results when taken as a whole and compared to the results exhibited by FLONASE® are not considered to demonstrate anything surprising or unexpected, as has been explained in previous office actions. Thus, Applicant's formulations are not considered to exhibit unexpected or surprising results either.

Regarding the recited particle size distribution, it has already been established that optimization of particle sizes is routine in the field of inhalable formulations (i.e. both oral and nasally administered). Thus, finding the optimal particle size and particle size distribution for a given particulate formulation is routinely practiced in the art and as applied to the combined prior art, would reasonably be expected to yield the same or a substantially similar particle size distribution as claimed by Applicants. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed August 13, 2009 have been fully considered but they are not persuasive. Applicants' have traversed the instant rejection by arguing that neither FLONASE or Bernini teach, suggest, or render predictable (1) aqueous formulations comprising 0.04% to 0.06% w/w suspended solid fluticasone particles, (2) the recited particle size distribution, (3) aqueous formulations comprising 0.04% to 0.06% w/w suspended solid fluticasone particles in combination with an antifungal agent as recited in claim 1, (4) Bernini is silent regarding the particle size necessary for targeting the nasal mucosa, and (5) Applicant's claimed formulations exhibit unexpected results and the Office has overlooked the statement in copending application 10/414,682 describing the comparison of Dey-FP with FLONASE® that Applicant's formulation exhibited an improvement in the magnitude of the TNSS.

The Examiner respectfully disagrees with Applicant's traversal arguments. Regarding (1), it is conceded that FLONASE teaches an aqueous formulation comprising suspended solid fluticasone particles in an amount of 0.0375% w/w. However, it is noted that when the amount of fluticasone propionate taught by FLONASE® is reported to the same number of significant figures utilized in Applicant's claims for the amount of fluticasone, this amount would be 0.04% w/w. Therefore, it is reasonable to conclude that the amount of solid fluticasone particles present in FLONASE would exhibit the same or substantially similar physiological effects as the amount of solid fluticasone particles recited in Applicant's claims. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection, when the amount of suspended fluticasone particles taught by FLONASE® is compared with the amount recited in Applicant's claimed based on the same number of

significant figures. MPEP § 2144.05. A prima facie obvious case of obviousness also exists when the prior art range is very close to the recited range, and the ordinary skilled artisan would reasonably expect both values to exhibit the same or substantially similar properties. MPEP § 2144.05. It is noted that Applicants admit on page 9 of their remarks/arguments that that the only difference between the tested fluticasone formulations and FLONASE® is the recited particle size distribution. As a result, Applicant's argument (1) is a frivolous argument, because Applicant acknowledges that this is not a point of difference between FLONASE® and the claimed formulations.

Regarding (2), it is the Examiner's position that optimization of particle sizes is routine in the field of inhalable formulations (i.e. both oral and nasally administered). Finding the optimal particle size and particle size distribution for a given particulate formulation is routinely practiced in the art and as applied to the combined prior art, would reasonably be expected to yield the same or a substantially similar particle size distribution as claimed by Applicants. Thus, absent a showing of unexpected results, the instantly recited particle size distribution is not considered to represent non-obvious modification of the prior art, but rather merely the routine optimization of a known result effective parameter.

Regarding (3), an ordinary skilled artisan would have been motivated to modify FLONASE® to incorporate a therapeutically effective amount of an anti-fungal agent and/or an antibacterial to obtain a composition suitable for treating not only the inflammation resulting from an infection, but also suitable for treating the underlying cause of the inflammation (i.e. a fungal and/or bacterial infection). An ordinary skilled artisan would have had a reasonable expectation of success upon modification of the FLONASE®/Bernini composition to further

comprise an anti-fungal or antibacterial agent because these are art-recognized therapeutics for treating fungal and bacterial infections and are known to be used in combination with anti-inflammatory steroids.

Regarding (4), Applicant is correct that Bernini does not expressly teach a particular particle size for targeting the nasal-paranasal mucosa. However, the particle sizes suitable for targeting the nasal-paranasal mucosa are known. For example, Osbakken teaches that the aerosolized anti-infective particles are surprisingly effective when they have a mass median aerodynamic diameter (MMAD) of about 1.0 to 5.0 microns [0081] and that the aerosolization/atomization of the formulations for nasal inhalation by a patient will result in liquid aerosol cloud particles having a MMAD of preferably between about 0.5 microns and 10 microns. The particle sizes identified by the prior art for nasal inhalation (Osbakken) overlap with the particle sizes recited in Applicant's claims. Thus, although a single reference relied upon in the instant application does not expressly teach a particular particle size or particle sizes for nasal inhalation, the appropriate particle sizes for targeting the nasal-paranasal mucosa were well known in the art, as evidenced by the teachings of the aforementioned combined prior art (Osbakken).

Regarding (5), it is unclear whether 50 mcg of fluticasone correlates with 0.04% w/w fluticasone or some other weight percentage. It is also noted that the data points are not displayed with error bars. The display of the uncertainty in the data points is deemed necessary because the data reported in Figures 1-4 are based upon a least squares mean analysis of the raw subjective Total Nasal Symptom Scores (TNSS) (i.e. these are aggregate data) manipulated using the ANOVA model. For this reason, wherein Applicants' data for the invented compositions and

the prior art data points are very similar in magnitude, it would be reasonable for one to conclude that these data points are the same within a margin of error. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention. The instant rejection is maintained.

Claims 71-74 **remain rejected** under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (1999, pp 445-446), in view of Bernini et al. (U.S. Patent No. 6,464,958), and Osbakken et al. (US 2002/0061281), as applied to claims 1, 4-6, 10-13, 22-25, 27-30, and 35 above, and further in view of Doi (U.S. Patent No. 6,368,616) and Meade (U.S. Patent No. 6,608,054).

Applicant Claims

Applicant claims a formulation as described above in the instant application further comprising a complexing agent (e.g. sodium edetate)

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of FLONASE®, the PDR®, the DIH, Bernini and Osbakken are restated above in the instant office action.

Doi teaches aqueous suspensions for nasal application and that the compositions may contain additives which are broadly used in nasal drops, such as preservatives, buffers (e.g. **citric**

acid), stabilizers, chelating agents (e.g. **citric acid and editic acid**), pH control agents (e.g. **citric acid**), etc. (title; abstract; col. 2, lines 61-65; col. 3, lines 8-17). The term "chelating agent" is synonymous with "complexing agent."

Meade teaches that sodium edetate and citric acid are known complexing agents (col. 9, lines 22-34).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

FLONASE® lacks the teaching of compositions further comprising a complexing agent. This deficiency is cured by the teachings of Doi or Meade, which have been provided as supporting documents to show that complexing agents are conventional ingredients in aqueous nasal formulations.

Finding of Prima Facie Obviousness Rational and Motivation *(MPEP §2142-2143)*

It would have been prima facie obvious to an ordinary skilled artisan at the time of the instant invention to modify the FLONASE®/Bernini/Osbakken compositions to further comprise a conventional additive broadly used in the formulation of nasal compositions, such as complexing agents. Regarding the specific complexing agent used, an ordinary skilled artisan would have been motivated to utilize any of the well-known complexing agents routinely utilized in aqueous nasal formulations (e.g. EDTA, sodium edetate, citric acid, etc.). An ordinary skilled artisan would have had a reasonable expectation of success, because the addition of complexing agents to aqueous formulations (e.g. nasally administrable aqueous suspensions) is conventional

in the art. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 8/13/09 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by presenting the same and/or similar arguments as were rebutted in the previous rejection. Thus, the Office's rebuttal arguments are herein incorporated by reference. The rejection is considered to remain proper and is maintained.

Claims 75-76 **remain rejected** under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (1999, pp 445-446), in view of Bernini et al. (U.S. Patent No. 6,464,958), and Osbakken et al. (US 2002/0061281), as applied to claims 1, 4-6, 10-13, 22-25, 27-30, and 35 above, and further in view of Walker ("Management of allergic rhinitis", *Nursing Times,* 2003, *99(23)*, Abstract) and Hamuy et al.("Topical antiviral agents for herpes simplex virus infections," *Drugs Today*, 1998, *34(12)*, Abstract Only).

Applicant Claims

Applicant claims a formulation as described above in the instant application that additionally comprises a therapeutic amount of an antiviral agent selected from a group consisting essentially of acyclovir, famciclovir, valacyclovir, edoxudine, ganciclovir, foscarnet,

cidovir (vistide), vitrasert, and formivirsen, and in some embodiments further comprises a complexing agent (e.g. sodium edetate).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of FLONASE, the PDR®, the DIH, Bernini, and Osbakken were restated above in the instant office action.

Walker teaches that viral and bacterial infection is the commonest acute cause of symptoms of allergic rhinitis (abstract).

Hamuy identifies several antiviral agents that have been used successfully to treat herpes simplex virus, including **cidofovir, edoxudine**, and penciclovir (abstract).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

FLONASE® lacks the teaching of compositions comprising an antiviral agent and an antibacterial agent. The antibacterial agent deficiency is cured by the teachings of Osbakken (see Table 1). The antiviral agent deficiency is cured by the teachings of Walker and Hamuy, which have been provided as supporting documents to demonstrate that viral infections are art-recognized to play a role in the etiology of rhinitis (Walker) and that cidofovir and edoxudine are well-known anti-viral agents (Hamuy).

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been prima facie obvious to an ordinary skilled artisan at the time of the instant invention to modify the FLONASE®/Bernini/Osbakken compositions to further comprise a known antiviral agent, such as cidofovir or edoxudine, because viral infections are known to play a role in the etiology of allergic rhinitis and cidofovir, edoxudine, acyclovir, ganiciclovir, foscarnet, and formivirsen are well-known antiviral agents. An ordinary skilled artisan would have had a reasonable expectation of success upon addition of a known antiviral agent, because viruses are known to play a role in the cause of acute allergic rhinitis and both cidofovir and edoxudine are known anti-viral agents. Regarding the particle size distributions recited in Applicant's claims, these have been addressed above in the previous rejections under 35 USC §103(a) and the relevant reasoning is incorporated herein by reference. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 8/13/09 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by presenting the same and/or similar arguments as were rebutted in the previous rejection. Thus, the Office's rebuttal arguments are herein incorporated by reference. The rejection is considered to remain proper and is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 **remains provisionally** rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/931,484 (copending '484) in view of Lacy, C. et al. 1999-2000 Drug Information Handbook, Lexi-Comp, Inc.: Cleveland, 1999, pp 561-563 and 568-569 (DIH) and Hebrecht, R. et al. "Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis" N. Eng. J. Med., 2002, 347(6), pp 408-415.

Independent claim 1 of copending '484 claims an aqueous suspension comprising (i) a suspended anti-inflammatory steroid particles, and (ii) about 20 to about 70 mg of an antifungal agent selected from the group consisting of itraconazole, ketoconazole, and voriconazole, wherein the anti-inflammatory steroid particles are characterized by a specific particle size distribution. Independent claim 1 of the instant application claims a formulation comprising an aqueous suspension of fluticasone particles (i.e. a suspension of an anti-inflammatory steroid)

characterized by a particle size distribution that overlaps with the particle size distribution of claim 1 of copending '484, and requires the presence of about 0.5 to about 150 mg of an antifungal agent.

The differences between claim 1 of the instant application and claim 1 of copending '484 are that claim 1 of the instant application has a different, but overlapping particle size distribution and does not specify any specific antifungal agents. The deficiency of specific antifungal agents is cured by the teachings of the DIH and Hebrecht, which establish that itraconazole (DIH, pg 561-62), ketoconazole (DIH, pgs. 568-69), and voriconazole (Hebrecht, see abstract, for example) are well-known anti-fungal agents. Regarding the amount of antifungal agent required by Applicant's claim 1, this amount encompasses the range recited in claim 1 of copending '484. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention.

Regarding the difference in the claimed particle size distributions, the physical characteristics (e.g. size and shape) of particulate compositions are clearly result specific parameters that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal

physical particle characteristics (e.g. MMAD, FPF, MMD, etc.) of a particulate composition needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of particle size distribution would have been obvious at the time of applicant's invention. Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claim 1 *prima facie* obvious over claims 1 of copending Application No. 11/931,484 (copending '484) in view of Lacy, C. et al. 1999-2000 Drug Information Handbook, Lexi-Comp, Inc.: Cleveland, 1999, pp 561-562 and 568-569 (DIH) and Hebrecht, R. et al. "Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis" N. Eng. J. Med., 2002, 347(6), pp 408-415.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 71-76 are rejected. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571)

272-5548. The examiner is on a flexible schedule, but can normally be reached on M-F ~10am~5:30 pm, and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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